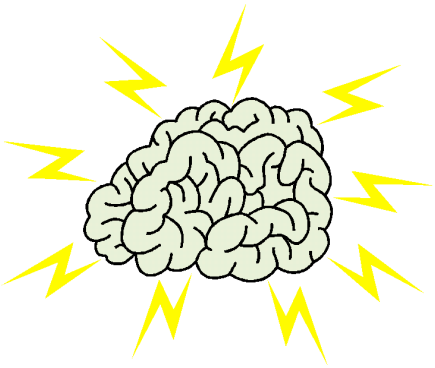
Riding the Spikes and Waves: Epilepsy Update



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Definitions

Seizure

The abnormal discharge of an aggregate of neurons that result in a change in behavior or normal function. More specifically, cortical neurons will be involved in a seizure.

Epilepsy

The condition of recurrent seizures. Epilepsy is a chronic condition, and a single seizure or several seizures during a short period of time may or may not represent epilepsy. Numerous diseases result in epilepsy. Seizures that are caused by toxins or other acute conditions and that do not occur at a later time do not constitute epilepsy.

Ictus

Refers to a seizure.
Interictal refers to the period between seizure, and postictal refers to the period following a seizure.

Aura

The symptoms that occur at the beginning of a seizure. The aura is part of the seizure and represents the consequence of an abnormal function of the neurons where the seizure begins. Aura comes from the Greek word meaning breeze.

Automatism

A motor behavior occurring during a state of clouded consciousness either during or after a seizure. Usually the patient is amnestic for this behavior. Automatisms may be a continuation of a pre-ictal activity or a new activity. More common automatisms include chewing motion, walking or running behavior, picking at clothing, and verbal behavior.

Impaired Consciousness

The inability to respond normally to exogenous stimuli.

Status Epilepticus

A seizure lasting longer than 30 minutes or intermittent seizures lasting longer than 30 minutes from which the patient does not regain consciousness.

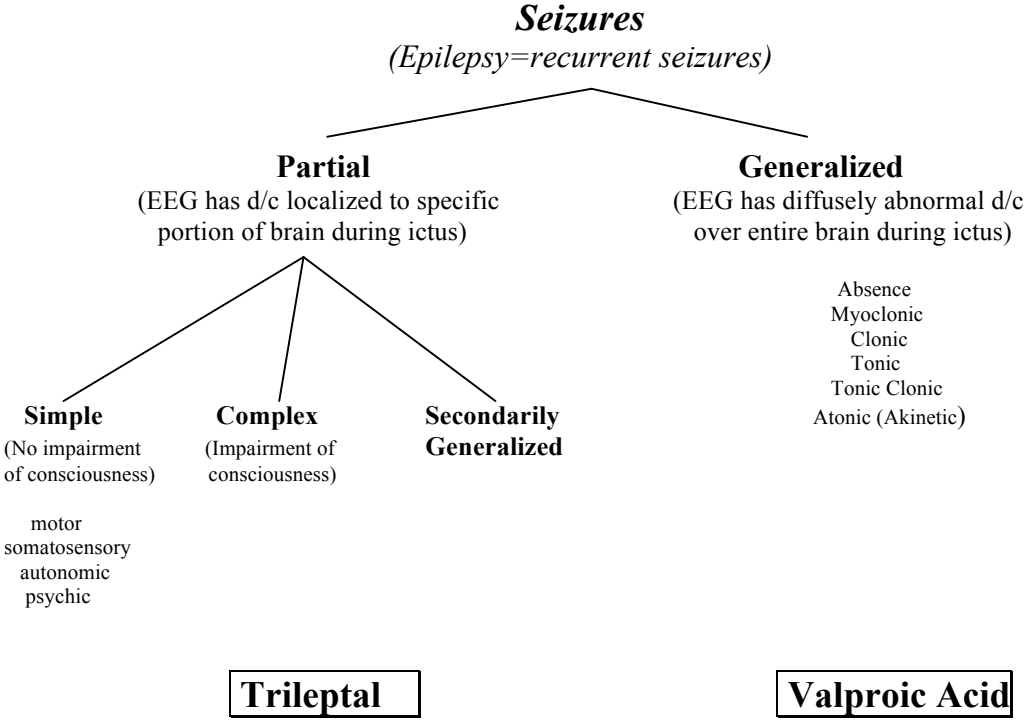
Classification of Seizures

Need for classification

There are many different types of epileptic seizures, each of which has certain identifying characteristics. There are also many epileptic syndromes that are characterized by the occurrence of a type (or types) of seizure(s), together with other features, such as etiology, age of onset, and evidence of brain pathology.

The classification of epileptic seizures and epileptic syndromes is of more than theoretical interest. Accurate diagnosis, which is aided by classification, allows the realization of such pragmatic goals as the most appropriate utilization of treatment, the judicious withholding of treatment, and the prediction of prognosis, which may lead to successful termination of treatment when appropriate. Of special importance to the clinician engaged in managing the treatment of the patient with epilepsy is the way in which accurate classification allows selection of the appropriate antiepileptic drug (AED) and the avoidance of contraindicated medications.

Today, many experts rely on the classification systems and epileptic syndromes developed by commissions organized by the International League Against Epilepsy (ILAE). Called the International Classification of Epileptic Seizures (ICES) and the International Classification of Epilepsies (ICE), these two classification systems are widely used and accepted.



International Classification of Epilepsy and Epileptic Syndromes

Epileptic syndromes are defined by clusters of signs and symptoms that customarily occur together. Features considered include predominant seizure type(s), age of onset, natural history, EEG, response to AEDs, etiology, family history, and prognosis.

The International League Against Epilepsy Classification of Epilepsy Syndromes of Childhood

Localization-Related Epilepsy Syndromes

Idiopathic (with age-related onset)
- Benign childhood epilepsy with centrotemporal (rolandic) spikes
- Childhood epilepsy with occipital paroxysms

Symptomatic or cryptogenic*
- Chronic progressive epilepsia partialis continua of childhood (Kojewnikow syndrome)
- Topographic syndromes (temporal lobe, frontal lobe, etc.)

Generalized Epilepsy Syndromes

Idiopathic (with age-related onset)
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (Janz syndrome)
- Epilepsy with grand mal seizures on awakening

Symptomatic or cryptogenic
- West syndrome (infantile spasms)
- Lennox Gastaut sydrome
- Epilepsy with myoclonic-astatic syndrome (Doose syndrome)
- Epilepsy with myoclonic absences

Epilepsy Syndromes Undetermined Whether Focal or Generalized

Severe myoclonic epilepsy in infancy (polymorphic epilepsy of infancy)
Epilpesy with continuous spikes and waves during slow wave sleep
Acquired epileptic aphasia (Landau-Kleffner syndrome)

Special Syndromes

Febrile Convulsions

*Cryptogenic epilepsies are presumed to be symptomatic and the etiology is unknown. They differ from the symptomatic epilepsies by only the lack of precise etiologic evidence. They may, in fact, be difficult or impossible to separate from some idiopathic epilepsies.

Examples of Epileptic Syndromes

Infancy

West Syndrome

Triad: infantile spasms, arrested psychomotor development, hysarrythmia.
Male>female; onset 4-7 mos, always < 12 mos.

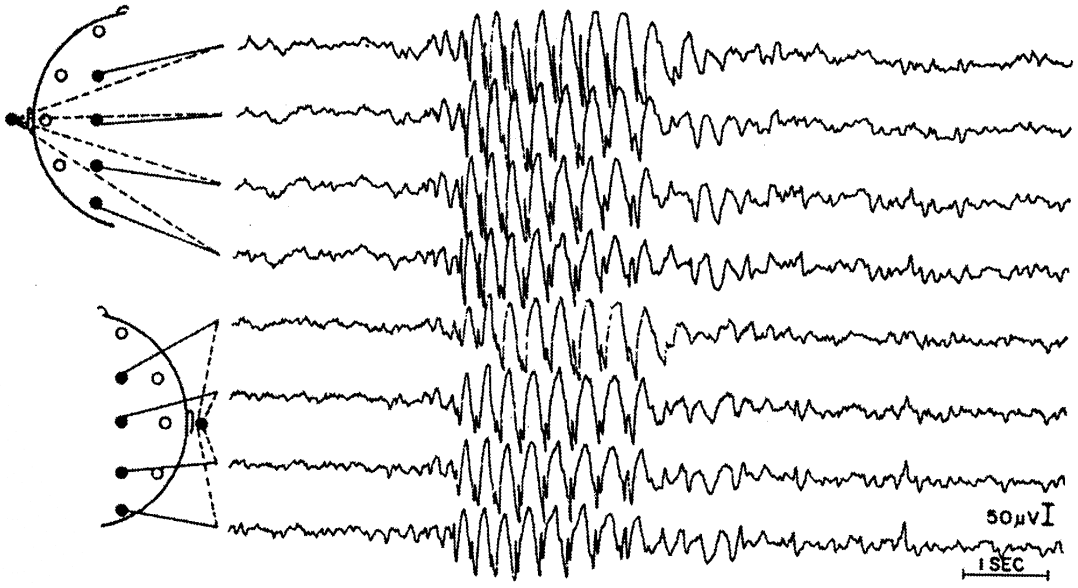
Childhood

Lennox-Gestaut Syndrome

Triad: mixed seizure disorder (tonic, atonic, atypical absence), myoclonic, GTC, partial), developmental delay/MR, and abnormal EEG pattern.
Onset 1-8 years.
Symptomatic and/or idiopathic.

Childhood Absence Epilpesy

Onset in childhood, before puberty, peak ages 6-7 years.
Seizures=absence, with or without clonic, atonic, tonic and autonomic components, and automatisms.
Development normal.
EEG=bilateral, synchronous, symmetric 3 Hz spike and wave activity: normal interictal background.
Frequency high: easily precipitated by hyperventilation.
Prognosis: good.
GTC components may develop in 40%.
Treatment: Ethosuximide, valproic acid (Preferred in GTC components present).



3 Hz Spike and Wave Activity characteristic of absence epilepsy

Benign Childhood Epilpesy with Central Temporal Spikes

Also known as Rolandic Epilepsy.
Onset: ages 3-13 years, peak at 9-10 years.

Seizures=simple partial, often involving the face, frequently with associated somatosensory symptoms; often generalized with nocturnal.
EEG=high-voltage central temporal spikes followed by slow waves, activated by sleep.
Genetic predisposition, male predominance.
Prognosis: excellent.

Acquired Epileptic Aphasia (Landau Kleffner Syndrome)
Childhood acquired aphasia=verbal auditory agnosia, rapid reduction of spontaneous speech.
Seizures=GTC, partial motor.
EEG=multifocal spikes, spike and wave discharges on EEG.
Prognosis: guarded; in general, seizures and EEG improve frequently before the age of 15.

Febrile Convulsions

Definition
Abnormal, sudden, excessive electrical discharge of neurons which propagates a neuronal process that affects end organs in a clinically measurable fashion, associated with a fever.

Criteria
The first convulsion by a child is associated with a temperature of >38 degrees Centigrade (>100.4 degrees Fahrenheit)

The child is less than 6 years old.

There is not evidence of CNS infection, inflammation, defined causes for the seizure, or metabolic disorder.

Classification
Simple
Lasts < 15 minutes.
No focal features present.
Occurrence of only one seizure in a 24 hour period.
Complex
Lasts > 15 minutes.
Focal features present.
Occurrence of a series with > one seizure in 24 hours.

Incidence
Occurs in 2-5% of all children.
Comprises 30% of all seizures occurring in children.
Age: 6 months to 5 years, with an average age of onset at 2 years.
Male>female; black>white.
Familial: 10% of parents of children with febrile seizures had a history of febrile seizures themselves, and 9% of siblings had at least one seizure in the past.

Relationship to meningitis
Most febrile seizures occur within the first 24 hours of onset of the fever.
If the seizure occurs more than 24 hours after the onset of the fever, suspect either meningitis or another specific neurologic or metabolic cause.
5-6% of patients with meningitis present with febrile seizures.
1:300 patients with febrile seizures actually have meningitis.

Natural History
Overall, 33% if children with febrile seizures will have recurrence of seizures.
Factors to be considered:
Neurologic status prior to the onset of the seizure (Increased risk if abnormal).
Character of the seizures (Increase risk if partial).

Family history of seizure disorders (Increased risk if family hx of epilepsy).
Age of onset of the disorder, which is considered to be the most important factor: 50% recurrence rate when onset is < 1 year. 28% recurrence rate when onset > 1 year.

90% of the recurrences will take place within 30 months of the initial seizure, with 50-75% occurring within the first year.

Risk of the development of epilepsy

In the general population: 0.5%.
Children who are developmentally normal with simple febrile seiures: 1.1%.
Children with neurologic deficits and complex febrile seizures: 15.4%.

Based on a study by Joffe and DeAngelis (AJDC, Dec. 1983), risk factors included: abnormal neurologic status, family hx of epilepsy, and complex febrile seizures. The risk of developing epilepsy was dependent on the number of risk factors in the history and on PE:

>2 factors: 13%
2 factors: 6%
1 factor: 3%
None: 2%

Neurologic sequelae

There are usually none.
One notable exception is complex febrile seizures that result in *prolonged* status epilepticus.
Neurological sequelae may include: motor or coordination difficulties, MR, learning disabilities, and behavior problems.

Treatment

Prophylactic long-term maintenance therapy

THE USUAL RECOMMENDATION IS **NOT** TO TREAT.
Factors that need to be considered include the aforementioned risk factors and the frequency of recurrence in an individual patient.
A patient with his/her first febrile seizure should NOT be considered for long-term therapy unless status epilepticus was the presentation.

The drug of choice: Phenobarbitol

Doses: 5 mg/kg/d
Therapeutic levels: 15-40 mcg/ml
Decreases recurrences by 40-70%.

Other drugs: Valproic Acid

This drug has been found to be effective in Europe for prophylaxis management of febrile seizures. However, it has not been formerly approved for this use in the US.

Acute intermittent treatment

Diazepam rectal gel (Diastat; pediatric formulation: 2.5 mg. 5 mg) approximately 0.5 mg/kg given at the onset of a convulsion.
This form of treatment is especially useful in the child prone to complex febrile seizures consisting of status epilepticus.

Use of low dose oral valium (0.2-0.33 mg/kg) has been studies without and with the use of antipyretic management. The results vary but overall it is felt that the potential side effects of the valium (ataxia, lethargy, irritability at 39%) can obscure serious symptoms in a patient who may develop a potentially serious infection such as meningitis.

Adolescence

Juvenile Myoclonic Epilepsy of Janz

Age of onset at or near puberty; male=female.
GTC sz or repeated myoclonic jerks upon awakening. Frequent myoclonic and absence spells during the waking state, especially precipitated by sleep deprivation, ETOH use.
Treatment: VPA. High risk of recurrence without rx, estimated to be 85%.

The First Non-Febrile Seizure

Clinical Dilemma

Distinguishing true seizures from non-epileptiform paroxysmal disorders of childhood.
Appropriate evaluation.
Whether to start treatment.

Differential Diagnosis of Seizures

Neonatal

Apnea
Hypoglycemia
Brainstem release phenomenon
Benign myoclonus

Infancy and Early Childhood

Breathholding spells
Spasmus nutans
Benign paroxysmal vertigo
Night terrors, sleep walking
Cyclic vomiting
Shuddering attacks
Masturbation
Sandifer's syndrome
Acute choreoathetosis

School Age

Migraine
Syncope
Tics
Paroxysmal Choreoathetosis
Dystonia
Episodic dyscontrol
Pseudoseizures

Physical and Neurological Examination

Signs Suggesting an Etiology for Seizures

System	Sign	Disorder
General examination	Dysmorphic features	Brain malformation, storage disease, syndrome, chromosomal abnormality
Head	Macrocephaly	Storage disease, phakomatoses, syndrome, obstructive hydoceph.

	Microcephaly	Hx of congenital infection, syndrome, hx of previous CNS injury, acquired neurodegenerative process
Hair	Broken, alopecia	Menkes disease, biotin deficiency, arginsuccinic aciduria
Skin	Hypopigmented macules, café-us-lait spots, upper eyelid hemangioma, petechiae, rash	Tuberous sclerosis, neurofibromatosis, Stuge-Weber, blood dyscrasias, meningitis, sepsis, autoimmune disorder
Neck	Nuchal rigidity	Meningitis, subarachnoid hemorrage, posterior fossa mass
Fundi	Papilledema. Hemorrhage	Tumor, trauma, child abuse, hypertensive encephalopathy
	Choreoretinitis, retinal lesions	Intrauterine infection, degenerative disease, tuberous sclerosis
Abdomen	Organomegaly	Storage disease
Nervous System	Altered mental status	Post-ictal vs metabolic disorders, systemic disorders, drug intoxication
	Focal neurologic findings	Tumor, hemorrhage, Todd's paralysis, stroke, head injury

Laboratory Evaluation

The following laboratory studies should be considered when a patient presents to the ER after a first time seizure, especially if the patient has not yet returned to his/her baseline:

CBC with differential
Lytes, Cr, Glu, Ca

Consider, if clinically appropriate to presentation:
LFT, Ammonia
TFTs
Urine toxicology screen
Serum amino acids, urine organic acids
Lumbar puncture: infection, subarachnoid hemorrhage

EEG
Should be arranged as an outpatient within two to four weeks after presentation.

Imaging studies

A CT scan is NOT always necessary in the patient who presents with his/her first seizure.

A CT scan in the ER should be considered in patients who:
Remain post-ictal or encephalopathic,
Had any focal features to the presentation of their seizure, or
Have any focality noted on neurologic examination.

Otherwise, arrangements for an EEG should be made within the next two weeks. Further imaging studies can then be arranged if the EEG demonstrates any focality.

In general, when imaging studies are necessary in patients with seizures, Magnetic Resonance Image (MRI) is the preferred study.

Risk of recurrence after the first seizure

The percentage varies in the literature, but tends to fall in the range of 35-60%.

Factors that increase the risk of recurrence include:
A clinical description of partial seizures
Presence of a focal abnormality detected by neurologic exam or CT/MRI
Presence of epilpetiform activity on EEG
A strong family history of epilepsy.

The majority of seizures (75%) will recur within 6 months, 87% within 1 year, and 96% within 2 years.

Treatment

The first afebrile seizure is usually *NOT* treated with AEDs.
However, an EEG is always ordered.
A formal consult with a neurologist is usually not necessary.

Factors to consider in the decision to initiate treatment include:
Age of the patient
Type of seizure
Predisposing factors
Psychologic and social consequences of further seizures
Change of recurrence of seizures
Risks of treatment: labeling, cost, side effects.

Limitations of activities

Driving

Varies from state to state.
In California, when a patient ***14 years of age*** or older presents to a physician with any form of alteration of consciousness, including partial complex and generalized seizures, that physician is bound by law to report the incident to the State of California Department of Motor Vehicles. Failure to do so can result in a significant fine ($10,000).

The report can be done by completing the ***Confidential Morbidity Report Form*** obtained from the Department of Public Health Services within the local county. The report can also be provided by filling out *a* ***Driver Medical Evaluation Form*** obtained from the DMV< or sending a letter directly to the local DMV office.

The power to suspend a license is under the jurisdiction of the California DMV. In most cases, the license is suspended until the physician feels it is safe for the patient to drive. The ***Driver Medical Evaluation Form*** is obtained by the patient from the DMV and completed by the physician. In California, there is no absolute time that a patient must be seizure-free, although most neurologists use the time frame of 6 months.

If the patient does undergo successful treatment with AEDs, he/she must also demonstrate compliance with medication by proof of appropriate refills, drug levels, and keeping appointments.

Other activities

Since the risk of recurrence is highest during the first six months after the first seizure, some "common sense" precautions should be followed:

The patient should shower/bath in the house only when someone is in the home in the event the seizure would result in alteration/loss of consciousness.

The patient should not swim or use a hot tub without supervision.

The patient should limit activities that require him/her to climb high places, when possible.

Helmets should be worm when biking or rollerblading.

Principle of Anticonvulsant Management

Anti-epileptic drugs (AEDs) should only be considered in a patient who has had more than one seizure in the afebrile state and in patients with febrile seizures who have been considered to be at high risk for recurrence.

Choice of medication depends on the seizure type and epileptic syndrome.

The monotherapy "game plan."
Once a medication has been chosen, start the medication at the recommended starting dose and interval (see drug charts). Obtain baseline labs prior to starting medication.

Obtain serum blood levels and labs that need to be monitored after five half-lives of the individual drug. Achieve therapeutic levels; adjust accordingly.

Continue to increase the does of the medication as needed to either achieve therapeutic benefit (i.e. seizure-free status) or drug toxicity occurs. Unacceptable side effects should include behavior and cognitive changes that might compromise the patient's quality of life.

Once an acceptable dose and therapeutic level has been achieved, monitor levels and labs every three months for the first year and every six months the second year.

When polytherapy is needed.
If the patient continues to have seizures despite high therapeutic drug levels, then a second drug should be added.

Begin the second drug at the recommended starting does and interval, while continuing the first drug. The first drug may need to be reduced slightly in does if anticipated side effects occur due to drug-drug interactions (see chart below). For example, adding valproic acid to a patient already on phenobarbital will usually increase the phenobarbital levels, causing unacceptable side effects such as sedation.

Pharmacokinetic drug interactions of antiepileptic drugs commonly encountered in practice

Original Drug	Added Drug	Effect of added drug on serum concentration of original drug
Carbanazepine	Phenobarbital	↓
	Phenytoin	↓
	Primidone	↓
Phenobarbital	Carbamazepine	No change
	Methsuximide	↑
	Phenytoin	↑
	Valproic Acid	↑
Phenytoin	Carbamazepine	↑
	Methsuximide	↑
	Phenobarbital	No change
	Primidone	No change
	Valproic Acid	↓
Primidone	Carbamazepine	↑of derived Phenobarbital
	Phenytoin	↑of derived Phenobarbital
	Valproic Acid	↑
Valproic Acid	Carbamazepine	↓
	Phenobarbital	↓
	Phenytoin	↓
	Primidone	↓

Wait five half-lives for the second drug, re-check blood levels and labs, and if the new drug is therapeutic and patient is seizure-free, begin wean of first drug. Re-check levels after patient is completely off first drug.

If seizures continue on two drugs, push the second until therapeutic benefit is achieved or side effects become unacceptable.

If a patient has been unsuccessfully managed on two different medications, a neurologist should be consulted

Who is a candidate for weaning off medication?

Any patient who has remained seizure free for at least two years.

Neonatal seizures are an exception. The patient can be considered for a wean off medication if seizure free any time during the first year. The earlier the better, depending on the neurologic status of the child and the cause of the neonatal seizure.

How to wean medication.

Withdrawal of medication should be done slowly.
One should try to reduce at a rate no faster than 1 tablet every five half-lives.
Designing a reduction plan that is easy for the patient to remember and comply is always best, i.e. descreasing by one tablet every other Monday until off.

What is the patient's risk of recurrence?

This is dependent on the type of seizure, the type of epileptic syndrome and other factors that include the neurologic status of the patient, the MRI results, and the EEG results at the time weaning is considered.

In general, the risk of recurrence is estimated to be at approximately 25-30%.

The risk of recurrence is higher in patients with partial seizures than in patients with primary generalized epilepsies.

The risk is higher in some forms of epileptic syndromes such as Juvenile Myoclonic Absence or Lennox Gestaut, and lower in others such as Childhood Absence and Rolandic Epilepsy.

The risk is also higher in patients with symptomatic epilepsies: i.e. Tuberous Sclerosis, Sturge Weber Disease, congenital migrational malformations such as heterotopias, schizencephaly, etc.

Finally, the risk is higher in patients with EEG abnormalities that are epileptiform at the time of consideration for withdrawal. However, an EEG should not be the basis for the decision to wean medication, not should it be ordered prior to wean unless the information is to be used to help make the decision.

What to instruct the patient while weaning medication.

The risk of recurrence is highest during the first six months after coming off the medication. Therefore, certain "common sense precautions should be followed:

If the patient is of driving age, he/she should be instructed not to drive for six months.

The patient should shower/bath in the house only when someone is in the home in the event a seizure that would result in alteration of consciousness occurs.

The patient should not perform activities that require him/her to climb high places.

Helmets should be worn when biking, rollerblading, or skateboarding.

The patient should not swim or enter a hot tub without supervision.

Treatment Options in Patients with Epilepsy

Anticonvulsant Drugs

Banzel
Barbituates: Phenobarbital, Primidone
Dilantin
Tegretol
Valproic Acid
Benzodiazepines: Valium, Ativan, Clonopin, Tranxene, Nitrazepam
Ethosuccimide
Methsuximide
Gabapentin
Lamotigine
Topiramate
Levatiracetam
Oxcarbazepine
Zonisamide
Felbamate
Vigabatrin
Vimpat

Adjunctive medications

Acetazolamide

Used occasionally for refractory generalized epilepsies, especially atypical absence, myoclonic, and akinetic spells, always in conjunction with other medication.
Dose: 250-1000 mg/day ÷ BID to TID

Tablets: 125, 250mg
Capsules: 500 mg

Steroids

ACTH

The first drug of choice for infantile spasms.

Treatment per protocol (consult a neurologist).
Acthar gel preferred over lyophilized powder.
ACTH is now an orphan drug; thus to obtain ACTH one must now contact NORD regarding their Acthar Gel Limited Access Program. It may take up to three days to obtain the drug.

NORD Acthar Gel Program: 1-800-459-7599

Prednisone

Preferred to ACTH by some epileptologists for infantile spasms.
Rarely and occasionally used in certain refractory epilepsies such as Landau Kleffner Syndrome, and Epilepsia Partialis Continua.
1-2 mg/kg
Given for 4-6 weeks; should be gradually discontinued over several weeks.

Ketogenic Diet

Currently the diet is utilized in children with any type of seizure disorder, especially when traditional medication in combination have proved ineffective or the side effects intolerable.

The ketogenic diet is a rigid, mathematically calculated, and doctor supervised diet. The diet is planned to produce ketosis by reversing the usual ratio of dietary carbohydrate and fat.

The diet is generally not used in children less than 1 year of age due to the difficulty in maintaining ketosis and euglycemia.
The diet most likely would not work for a child who has access to food or has very specific food preferences. The diet would also not work for a child whose meals are prepared and eaten outside the home.

Kaiser Permanente of Northern California has a *Ketogenic Diet Program,* which is implemented by the child neurologist and requires initial hospitalization in Hayward. The patient will then need closed follow-up by the pediatric neurologist, pediatrician, and dietician in charge of the program.

Vagus Nerve Stimulation

A vagus nerve stimulator is surgically implanted into the patient by either an ENT physician or neurosurgeon. The voltage of the stimulator is gradually increased over time by either a neurologist or epileptologist. The stimulator gives the vagus nerve electrical stimulation at fixed intervals (i.e. every five minutes) and fixed voltage.

This treatment has been studied and used for children and adults with refractory generalized and partial epilepsy, and with drop attacks and Lennox—Gestaut Syndrome. The mean reduction in seizures averages about 58%, with 21% of the patients having a > 90% reduction in sz frequency.

Surgical Treatment of Epilepsy

Surgery is sometimes recommended for children with epilepsy that in intractable to optimal anticonvulsant therapy. Surgery is never a substitute for good medical therapy, and anticonvulsant drugs are often needed after surgery is performed.

Three procedures are often used: hemispherectomy, interhemispheric commissurotomy, and temporal lobectomy.

Evaluation for such procedures is extensive, requiring the services of a specific epilepsy center.

Such evaluation may include hospitalized telemetry monitoring of seizures, placement of sphenoidal and subdural transcortical electrodes, PET scanning, and extensive neuropsychological testing.

Anticonvulsant Medications

DRUG	FORMS	DAILY DOSAGE	LABS	USES	SIDE EFFECTS	COMMENTS
Carbamazepine (Tegretol) Tegretol XR Carbatrol	100 mg/5 ml 100 mg chew. tab 200 mg tab 100, 200, 400 mg tabs 200 & 300 mg extended release capsules	10-30 mg/kg/d up to 800-200 mg/kg/d divided bid-qid	CBC, Na, SGPT, trough level 1 week after starting; then q 3-6 mos	Simple and complex partial sz, GTC sz	Drowsiness, GI upset, ataxia, diplopia, dizziness, leukopenia, hepatotoxicity, hyponatremia, vestibulopathy, rash/allergy, aplastic anemia.	Can make absence seizures worse. Avoid EES, theophylline, cimetidine, clarithrmycin, fluoxetine, isoniazid, verapamil—will ↑ CBZ level. Troughs: 4-12
Valproic Acid (Depakene) Divalproex (Depakote) Depakon (IV form)	250 mg/5cc 125 mg sprinkle 250 mg & 500 mg tabs 100mg/cc in 5ml vials; infuse at 20 mg/min over 60 min.	PO 12-60 mg/kg/d up to 1000-2000 mg/d divided bid-quid. Rectal Use syrup diluted 1:1 with water, given PR as retention enema. Use same po daily dose ÷ q 6 hours. Convert back to po as soon as possible.	CBC, SGPT, Cr Trough level 1 week after starting; then q 3-6 mos	GTC, absence, akinetic, myoclonic, and partial szs	GI upset, diarrhea, weight gain, tremor, hair loss, macrocytosis, thrombocytopenia, pancytopenia, plt dysfunction, hepatotoxicity, hyperammonaemia, teratogenic—most common= spina bifida	In all children < 2yrs, use with L-carnitor 100 mg/kg/d up to 1000 mg/d. Thrombocytopenia risk with infections, responsive to ↓ dose. Trough: 40-150 (usually 70-100)

Rufinamide (Banzel)	200 mg tabs 400 mg tabs	45 mg/kg/d divided BID Start 10 mg/kg/d po BID, increasing by 10 mg/kg qod to 45 mg/kg/d divided BID Max: 1600 mg BID	None	Lennox-Gestaut Syndrome	Depression, behavioral changes, suicidality; s/sx hypersensitivy reaction if rash develops; leucopenia, Somnolence, vomiting, headache, fatigue, dizziness, nausea, tremor, nystagmus, blurred vision	Modulates the activity and prolongs the inactivity of the sodium channel
Phenytoin (Dilantin) Fosphenytoin (Cerebrex)	30 mg/5cc 125 mg/5cc 50 mg chew tab 30 & 100 mg cap 50 mg phenytoin equivalent (75 mg fosphenytoin)/1 cc (2, 10 ml)	4-8 mg/kg/d up to 300-500 mg/d divided qd-tid All doses are expressed as phenytoin sodium equivalents (PE): 1 mg phenytoin = 1 mg PE.	CBC, SGPT, tough level 1-2 wks after starting and q 3-6 mos	Simple and complex partial, GTC.	Sedation, gingival hyperplasia, hirsutism, ataxia, dizziness, nystagmus, hepatotoxicity, leukopenia, adenopathy, lupus-like syndrome, neuropathy	0 order kinetics and erratic absorption and metabolism make dosing in children difficult. ↑ szs with toxicity. Trough levels: 10-20. May be administered IV or IM; fewer administration adverse effects; expensive. *Fosphenytoin* Use with caution in patients with prophyria. Consider amount of phosphate delivered in pts with phosphate restrictions. May see hypokalemia with rapid IV infusion.
Phenobarbital	20 mg/5cc 10, 30, 60 & 100	4-8 mg/kg/d up to 90-120 mg/d	CBC, SGPT, tough level 1-2 wks after	GTC & partial szs, non-myoclonic szs	Sedation, paradoxical	Behavioral side effects limit use over age 2.

	mg tabs ¼, ½, 1 grain tabs	divided qd-bid.	starting, then q 3-6 mos.	in infancy.	hyperkinesis, mild reversible cognitive impairment, rash, ataxia	Level rises when VPA added. Trough: 15-40.
Primidone (Mysoline)	250 mg/5cc 50 & 250 mg tabs	10-25 mg/kg/d up to 500 mg/d divided bid-tid	CBC, SGPT, phenobarb trough level 2-3 wks after starting, then q 3-6 mos.	Same as Phenobarbital.	Same as Phenobarbital, headache, slowed speech.	Metabolized to Phenobarbital & PEMA, rapid & slow metabolizers. Trough: same as phenobarb.
Ethosuximide (Zarontin)	250 mg/ 5 ml 250 mg tab	10-30 mg/kg/d up to 1000 mg/d divided bid-tid	CBC, trough level 1-2 wks after starting, then q 3-6 mos.	Absence epilepsy without GTC szs.	GI upset, rash, lupus-like syndrome, headache.	Increase slowly to avoid GI upset. Trough: 40-100.
Methsuccimide (Celontin)	150 mg, 300 mg Kapseals	*Children PO* 10-15 mg/kg/24 hours ÷ q 6-8 hrs. Increase weekly to max 30 mg/kg per 24 hrs. *Adults PO* 300 mg/24 hr ÷ BID-QID for 1 wk. May ↑ by 300 mg/24 hr to max dose of 1.2 gm/24 hr ÷ BID-QID.	CBC, LFTs, UA About 1 wk after steady state and then q 3-6 mos.	Refractory absence epilepsy	GI symptoms, blood dyscrasias, mental status changes, periorbital edema, drowsiness, Stevens-Johnson syndrome.	Therapeutic range: 10-40 mg/L. Measure therapeutic range for metabolite, N-desmethylmethsuximide.

Benzodiazepines (Valium, Ativan, Klonopin, Tranxene, Nitrazepam) Diastat (rectal valium)	Varies by specific compound *Pediatric rectal gel* 2.5, 5, 10 mg (5mg/ml concentration with 4.4 cm rectal tip delivery system) *Adult rectal gel* 10, 15, 20 mg (5 mg/ml concentration with 6 cm rectal tip delivery system)	Varies by specific compound All doses rounded to nearest available dosage strength. 2-5 yrs: 0.5 mg/kg 6-11 yrs: 0.3 mg/kg ≥ 12 yrs: 0.2 mg/kg	If needed, trough level 1-3 wks after starting, then prn.	Add on for myoclonic, akinetic and mixed szs; may try in refractory partial szs; most helpful with status epilepticus.	Sedation, tachyphylaxis, dependence, excess drooling	Usefulness often limited by side effects. Expensive.
Gabapentin (Neurontin)	100, 300 & 400 mg tabs	600-900 mg/d divided tid	None	2nd line drug for partial szs. ? monotherapy for Rolandic Epilepsy.	Dizziness, GI upset, ataxia, aggressiveness, hyperactivity, irritability, somnolence, nystagmus, weight gain.	Side effects rare. Does not alter pharmacokinetics of other AEDs, expensive.
Levetiracetam (Keppra)	250, 500, 750 mg tablets	In children: consult a neurologist. In adults: 1000 mg/d divided bid; may increase by 1000 mg/d q 2	None	Adjunctive rx for partial szs	Asthenia, headache, infection, pain, dizzuness, somnolence	Reduce dosage in patients with renal impairment. Does not affect the plasma concentration of existing AEDs.

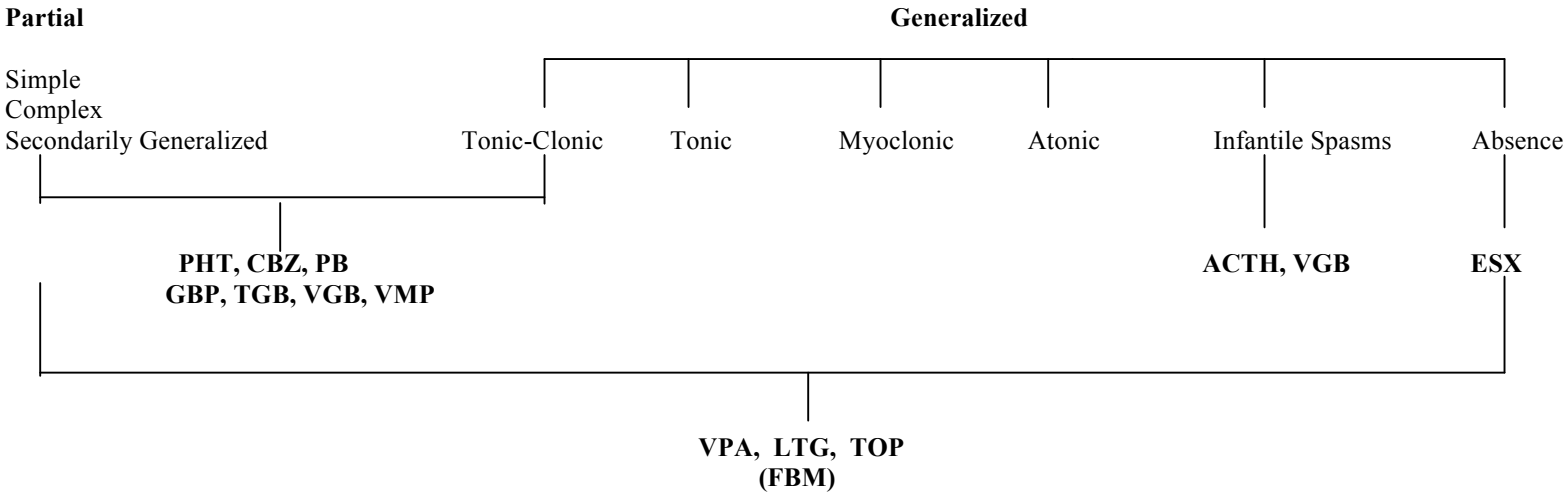
		wks to max dose of 3000 mg/d				
Lamotrigine (Lamictal)	25 mg chew tabs 25 & 100 mg tabs	1-20 mg/kg/d up to 200-600 mg/d divided tid. *Tricky: consult a neurologist.*	CBC & SGPT q 3-6 mos.	2nd line drug for partial szs, absence szs, Lennox-Gestaut, GTC, myoclonic, atonic.	RASH in 10-12%, life threatening rash in 1:1000 adults and 1:100-200 children, (↑ risk with rapid titration and adding to VPA), GI upset, fatigue, ataxia, dizziness, diplopia, headache, nausea, vomiting.	Prolongs t1/2 of VPA; need to increase slowly by 5-10 mg/kg; expensive; complicated pharmacokinetics with other AEDS which ↓ clearance of LMG—consult a neurologist.
Oxcarbazepine (Trileptal)	150, 300, 600 mg tablets 300 mg/ 5 cc	In adults: 600 mg/d divided bid; increase to max of 1200 mg/d divided bid In children: Start with 8-10 mg/kg/d divided bid; increase to max according to wt: 20-29 kg: 900 mg/d 30-39 kg: 1200 mg/d >40 kg: 1800 mg/d	None	Adjunctive rx, and monotherapy for partial szs in adults; Adjunctive rx for partial szs in children ages 4-16 yrs.	Dizziness, vomiting, fatigue, ataxia, double vision, nausea, GI distress, hyponatremia, headache, somnolence	Pts with allergic rxn to CBZ have 25-30% risk of same rxn with Trileptal. Can effect other AED levels; when added as 2nd agent, need to monitor levels of initial AED.
Topiramate (Topomax)	25, 100, 200 mg tab 25 mg sprinkles	1 mg/kg/d up to 3-10 mg/kg/d ÷ bid.	None	Partial szs, Lennix-Gestaut, infantile spasms.	Behavioral adverse effects, anorexia, sleep disorders, somnolence, dizziness, fatigue, headache, diplopia,	Nephrolithiasis reported in adult pts caused by ability of drug to inhibit carbonic anhydrase. Use with caution in children on ketogenic

					ataxia, psychomotor slowing, nystagmus, impaired concentration, weight loss, nephrolithiasis.	diet or taking acetazolamide.
Zonisamide (Zonegran)	100 mg capsules	Children < 16 yrs: Consult neurologist Adults: 100 mg/d; may increase q 2 weeks by 100 mg to max of 400 mg/d	None	Adjunctive rx for partial seizures	Headache, abdominal pain, anorexia, nausea, dizziness, somnolence, fatigue, speech abnormalities, diplopia	Has long t ½; may take up to 2 weeks to achieve steady state; Classified as a sulfonamide, therefore if allergic to sulfa meds, contraindicated.
Felbamate (Felbatol)	600 mg/5 cc 400 & 600 mg tabs	45 mg/kg/d up to 3600 mg/d divided bid-tid.	CBC, SGPT monthly.	Partial sz, atonic szs, Lennox-Gestaut, infantile spasms.	Anorexia, weight loss, vomiting, insomnia, headache, dizziness, somnolence, hepatoxicity, aplastic anemia.	Relatively high risk of aplastic anemia and hepatotoxicity severely restricts use to refractory cases. Inhibits metabolism of PHT, VPA, CBZ; need to ↓ other AEDs by 20-30%.
Vigabatrin (Sabril)	500 mg sachets	10-30 mg/kg/d divided tid.	None	Myoclonic, generalized, partial szs, infantile spasms; Lennox Gestaut. *Found to be especially effective in pts with infantile spasms & tuberous*	Gi upset, headache, Hyperactivity, weight gain, facial edema, drowsiness, insomnia, ataxia, stupor. *Retinopathy with longterm use.*	Not available in USA. Recently did not receive FDA approval due to visual field defects with long-term use. Some parents able to obtain outside of country. May be resubmitted for orphan drug status for

				sclerosis.		for rx of infantile spasms.
Tiagabine (Gabatril)	4, 12, 16, 20 mg tabs	0.1mg/kg/d; titrate upward as needed by 0.1 mg/kg every two weeks to max of 1.5 mg/kg/d ÷ bid to tid.	None	Partial szs; GTC; absence; atonic; myoclonic.	Somnolence, dizziness, headache, ataxia, depression.	Non-convulsive status or twilight state reported in adults receiving higher doses of tiagabine (48-60 mg/d). Little interaction with other AEDs.
Lacosamine (Vimpat)	50, 100, 150, 250 mg tablets 200 mg/20mL IV	50 mg po/IV bid, increase by 100 mg/day Max: 400 mg/day	Baseline Creatinine Baseline EKG if known conduction abnl	Partial seizure disorders	Multi-organ hypersensitivity rxn; PR prolongation; Syncope; atrial fibrillation and atrial flutter; suicidality; dizziness, headache, diplopia, N/V	Exact MOA unknown; Enhances slow inactivation of voltage-sensitive Na channels; stabilizes neuronal membranes, inhibiting repetitive firing
Steroids (ACTH & prednisone)	ACTH (Acthar) gel 80 u/ml Prednisone: many	Per protocol. Starting doses are: ACTH 150 u/m2/d, Prednisone 2 mg/kg/d; *Consult a neurologist.*	Per protocol; *consult a neurologist.*	Infantile spasms, myoclonic szs, refractory epilepsy, Landau-Kleffner Syndrome.	HTN, immunosuppression, hyperglycemia, hyperactivity, osteopenia.	Use in closely supervised protocols with neurologist; use limited to 3-6 mos.
Ketogenic diet			Per protocol	Refractory Epilepsy or alternative to AEDs when requested by parents.	Malnutrition, GI upset, lethargy, hypoglycemia, difficult to maintain in ambulatory	Use in closely supervised protocols with neurologist and dietician for 1-2 years.

					children.	
Vagus Nerve Stimulation	Surgical implantation of a vagus nerve stimulator.	Stimulator is adjusted to specific voltage at regular intervals by neurologist or epileptologist.		Refractory Partial Szs		Postulated effects: synchronization of brain activity; inhibition of epileptogenic structures; monoaminergic modulation of sz threshold; reduction of activity in the solitary nucleus.

Summary of Current Treatment Options



Status Epilepticus

A common pediatric neurologic emergency.
Affects 25-50,000 children in US each year.

Definition

A single seizure that lasts for at least 30 minutes, or recurrent seizures lasting for more than 30 minutes without the patient regaining consciousness.

Goals

- Ensure adequate cardiorespiratory function.
- Stop seizure activity.
- Prevent recurrence of seizures.
- Identify and treat the etiology.

Suggested Timetable for the Treatment of Status Epilepticus

Time (in minutes) from the onset of the seizure or arrival in ER	Action
0-5	Diagnose status epilepticus by observing the sz activity or if one additional sz has occurred without recovery in between. Administer oxygen by nasal cannula or mask; position the patient's head for optimal airway patency; consider intubation if respiratory assistance is needed. Obtain and record vital signs at onset of care and

	periodically thereafter; control any abnormalities as necessary; establish EKG monitoring. Establish IV access; draw venous blood samples for glucose level, serum electrolytes, Ca, Mg, CBC. Consider anticonvulsant levels, LFTs, blood cultures, toxicology screen, NH3 when clinically appropriate. Assess oxygenation with oximetry or periodic arterial blood gas determinations.
6-9	For established hypoglycemia or an unavailable blood glucose level, administer glucose: in adults: give 100 mg thiamine, followed by 50 mg of 50% glucose by direct IVP; in children: give 2 ml/kg of 25% glucose.
10-20	Administer either 0.1 mg/kg of lorazepam (Ativan) at 2 mg/min up to 4 mg total dose in adults. Less preferred alternative: 0.2 mg/kg of diazepam (valium) at 5 mg/min IV up to 20 mg maximum in adults. If diazepam used, can be repeated if seizure continues after 5 minutes. Diazepam use must be followed by loading with phenytoin.
20+	If status persists, administer fosphenytoin 20 mg PE (phenytoin equivalents)/kg at 3 mg/ kg/min (150 mg PE min/min maximum); if seizures continue, fosphenytoin 5-10 mg PE/kg up to maximum of 30 mg/kg. Alternative: Administer 20 mg/kg phenytoin no faster than 50 mg/min in adults and 1 mg/kg/min in children by IV; monitor electrocardiogram and blood pressure during infusion. IV fluid must be

	0.9% saline without glucose. NOTE: Phenobarbital, rather than phenytoin, may be used as the first AED of choice in children, 2 years old.
≥ 60	If status continues, give additional phenytoin or fosphenytoin at boluses of 5mg/kg (PE) to maximum of 30 mg/kg If status persists, give 20 mg/kg of Phenobarbital IV at max. rate of 60 mg/min in adults, 30 mg/min in children. *When Phenobarbital is given after a benzodiazepine, the risk of apnea or hyopnea is great and assisted ventilation is usually required.* If status persists, then combined aggressive therapy and thorough neurological evaluation are required. Such a patient requires admission to an ICU, urgent EEG recording, and administration of an intravenous anesthetic agent. Drugs available for such use include barbiturates, midazolam, and propofol. Intubation & ventilation is required, and vasopressors are frequently used. Midazolam anesthesia is initiated by 0.2 mg/kg IV that is followed by maintenance at 0.75 to 10 μg/kg/min. This dose variation is caused by tachyphylaxis. Both phenytoin and phenobarbital maintenance should be continued. Assessments with clinical evaluation and EEG must be performed at regular intervals. Barbituates are potent but associated with profound systemic effects. Sodium pentobarbital loading dose is 15 mg/kg OV given slowly over 1-2 hours, then continuous IV at 0.5-1.0 mg/kg/hr. During

	hours 0-6, may give additional loading doses of 5 mg/kg q 2 hours until a burst-suppression pattern on EEG is achieved. Propofol anesthesia is initiated with 1-2 mg/kg and then between 2-10 mg/kg/hr. Doses are adjusted based on effects of drug on EEG. Acute treatment endpoints are spike suppression or a pattern of burst-suppression with interburst intervals more than 1 second.

Modified from: Willmore, L.J., "Epilepsy Emergencies: The First Seizure and Status Epilepticus," *Neurology,* 1998; 51 5 Suppl 4): S34-S38.